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Index of tumor cells opens a new perspective to prevent cancer progression

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Researchers from the School of Medicine in Ribeirão Preto (FMRP), at the University of São Paulo (USP), in collaboration with international groups, have developed indices that provide information about the prognosis of cancers, aid in the choice of the most appropriate therapy and identify potential targets for the development of new drugs. Their paper, titled "Machine Learning Identity Stemness Features Associated with Oncogenic Dedifferentiation," will be published on April 5 in *Cell*.

To perform the study, researchers at the Omics laboratory from the Department of Genetics of the FMRP combined the use of artificial intelligence algorithms, genomic data from 12,000 samples from 33 different types of tumors, and an understanding of how progression of cancer occurs.

According to Houtan Noushmehr, senior author of the study, the methodologies used in this work are part of a new trend in biomedical sciences research to use the large amount of molecular data now available. "The present challenge is to manage, interpret and analyze different categories of data," says Noushmehr, "which requires researchers to integrate knowledge in biology, computer science and statistics." He considers the training of young scientists to manage these massive amounts of data as his main task, both as a teacher and a researcher.

These results build on the group's previous studies, including one also published in *Cell*, that identified important genomic features of brain

tumors. "The goal is that our index can be used one day in the clinical routine as additional information for the clinician to choose the most appropriate treatment for each patient and tumor," says Tathiane Malta, first author of the study. In addition to the Ribeirão Preto team, researchers from Harvard University in the United States and the University of Poznan in Poland contributed.

According to a currently accepted understanding, transformations that healthy cells undergo when growing tumors include mainly two characteristics: The loss of their specific features and the acquisition of the ability to multiply in a disorderly fashion. This process can also be considered as a loss of specialization, with tumor cells become progressively undifferentiated. Typically, the sub-population of cancer stem cells "drives" tumor growth. The stemness indices developed by the researchers provide a measure of how much the tumor cells resemble stem cells.

Based on the idea that there is a similarity between tumor cells and stem cells, the USP researchers used a machine-learning algorithm to detect and systematize molecular characteristics of healthy stem cells and differentiated cells derived from them. The software analyzed thousands of cells at different stages of differentiation, to identify typical molecular signatures of stem cells. With this information, they created two independent stemness-similarity indices based on gene expression and DNA methylation. The indices range from zero to one, with zero meaning low similarity to stem cells, and one high similarity.

The database from The Cancer Genome Atlas (TCGA) program includes samples from primary tumors of 12,000 people, covering 33 different types of cancers. Over the last 10 years, scientists involved in the program have generated and stored data on genetic and epigenetic changes in tumors. Using the stemness indices, the researchers detected the tumoral degree of stemness in the TCGA samples.

The main finding of the study is that stemness indices provide a measure of the path of tumor cells towards "de-differentiation," with higher indices correlating with tumor aggressiveness in many types of cancer. Accordingly, the researchers found that metastatic tumors have high rates of similarity to stem cells. In addition, the stemness indices could allow the identification of new targets for anticancer drugs, aimed at halting the progression of the cells towards de-differentiation. "If we can identify the point at which the tumor cells start to have characteristics of stem cells, we can prevent this trajectory and avoid its aggravation," Noushmehr adds.

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